*Aventis Bio-Services*

**Robert J. Kratzel, Ph.D., M.B.A.**
Director, Regulatory Affairs



Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

29 April 2002

**RE: Docket 01D-0584**
Draft Guidance for Industry: Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV

Dear Sir or Madam:

Aventis Bio-Services wishes to thank the FDA for the opportunity to comment on this draft guidance for industry. The development and implementation of NAT testing of pooled plasma has been a complex and evolving issue for the past several years, and this guidance document is an important and long awaited document.

Comments on the *Draft Guidance for Industry: Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV* must be preceded by a brief review of the first published guidance on NAT testing, the *Draft Guidance for Industry: Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma*, issued in November 1999. This document was issued in response to inquiries as to how the FDA intended to regulate nucleic acid testing of plasma pools. In this draft guidance FDA stated that nucleic acid tests should be licensed, that data supporting the effectiveness of such tests should be collected through clinical studies performed under an IND, and that this data should be submitted to support approval of the test under a BLA.



This document outlined several possible scenarios for the development of NAT tests. These included development of the NAT, including clinical studies conducted under an IND, by:

- a blood establishment
- a manufacturer of plasma derivatives
- a kit manufacturer
- an independent testing laboratory

Aventis Bio-Services, Inc. · 1020 First Avenue · P.O. Box 61501 · King of Prussia, PA 19406-0901 · www.aventis.com
Telephone (610) 878-4297 · Fax (610) 878-4025 · robert.kratzel@aventis.com

In this document the FDA also stated that the blood product manufacturer would be expected to file a supplement for each licensed product, and also presented four different regulatory approaches that could be used to obtain approval of a license for nucleic acid testing of pooled plasma. The four approaches included:

- **A blood product manufacturer assuming full responsibility for the testing**. Under this scenario the blood product manufacturer would file a BLA for licensure of the testing procedure. Other manufacturers who wished to use the test would file individual application supplements for each product, reporting the testing to FDA as a manufacturing change.
- **A manufacturer of a blood product could send plasma or small pools of plasma to an independent testing laboratory.** The independent laboratory would be expected to file a BLA in support of the licensure of the testing procedure. Blood product manufacturers who wished to use this independent laboratory would submit individual application supplements for each product for which the licensed nucleic acid test would be used.
- **A blood product manufacturer might develop an in-house nucleic acid test, with an arrangement to have reactive samples retested by an independent testing laboratory.** FDA would regard this arrangement as shared manufacturing. The blood product manufacturer would submit preclinical data and evidence that the "in-house" nucleic acid test was no less sensitive, analytically, than that of the "outside" test laboratory and would be responsible for control of the "in-house" reagents. Both the blood product manufacturer and the independent laboratory would conduct studies under either a joint or separate INDs. The independent laboratory would submit a BLA for licensure of the "outside" test and the blood product manufacturer would submit a BLA supplement for the "in-house" test. The combined tests would be licensed under shared manufacturing for use as a donor screening test.
- **A nucleic acid test kit would be developed independently and shipped for use by a blood product manufacturer.** In this case, the test kit manufacturer would file an IND, followed by a BLA, either jointly with the blood product manufacturer or separately

It should be noted that the regulatory guidance provided in this early draft guidance document (which has not yet been issued as a final guidance document) is general in nature, and refers to a "BLA for licensure of the testing procedure" (testing procedure is not specifically defined) and refers to "individual application supplements for each product" (no guidance regarding the type of supplement, e.g., PAS or CBE-30, is provided).

Industry has anticipated receiving further guidance on the licensing requirements for NAT testing, however, the *Draft Guidance for Industry- Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission*

*of HIV-1 and HCV* does not provide the clarification or details that are needed in order to submit the proper license supplements prior to implementing a licensed NAT for HIV-1 and HCV. This draft guidance document lacks substance when compared to the more recently released equivalent document that addresses NAT of blood products for transfusion (*Draft Guidance for Industry - Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components for Transfusion to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV*). With the understanding that there will be differences in the requirements for NAT of Source Plasma and blood products for transfusion, the two documents should be harmonized, at least in terms of format and content.

Specific comments and/or suggestions follow:

**Use of a licensed test**

The guidance document requires that all establishments engaged in the manufacture of Source Plasma submit "pre-approval" (i.e., prior approval) BLA supplements for the use of an approved nucleic acid test in accordance with 21 CFR 601.12 (b) by June 1, 2002, However, at this time the only licensed tests that are available are the tests developed by National Genetics Institute (NGI). The use of the term "BLA supplement," rather than "BLA for licensure of the testing procedure" implies that every Source Plasma manufacturer would have to submit by 01 June 2002 a supplement describing how they will implement the NGI tests.

This is not realistic for several reasons:

1) NGI may not be able to test all the Source Plasma that is collected in the U.S. within a reasonable timeframe.
2) Given the information that is available at this time, six months would not be an adequate period of time for all Source Plasma manufacturers to make arrangements with NGI to provide this service.
3) What is considered as the NGI "testing procedure" is not adequately described – for example, whether or not NGI's pooling laboratory (located in California) is considered as part of the NGI testing procedure has not been clear. If it is not considered as part of the licensed testing procedure, then appropriate guidance regarding the requirements and possible options for pooling of Source Plasma samples should be provided.
4) No guidance as to the content of the prior approval supplement is provided. The supplements that would be required by the *Draft Guidance for Industry- Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV* would all fall under the second scenario that is presented in *Draft Guidance for Industry - Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma,* i.e., "A manufacturer of a blood product could send plasma or small pools of plasma to an independent testing laboratory. The independent laboratory would be expected to file a BLA in support of the licensure of the testing procedure. Blood product manufacturers

who wished to use this independent laboratory would submit individual application supplements for each product for which the licensed nucleic acid test would be used." The requirements for the prior approval supplement for this type of situation should be described for industry. There appear to be only two possibilities – either a Source Plasma manufacturer could send samples to NGI for pooling and testing, or the manufacturer could elect to perform the pooling of samples, and then send the pools to NGI for testing. In either case, the information, e.g., SOPs, validation protocols and/or data, etc. that would be required in the license supplement should be clearly described. There are many possible scenarios, and knowledge of the regulatory requirements for the various options could aid in the selection of an appropriate testing process.

**Time for Implementation**

The draft guidance states that a license supplement must be submitted by a certain date (June 1, 2002). The requirement could also be stated in terms of implementing a licensed test within a given number of months of the date of the final guidance document. This would be consistent with the *Draft Guidance for Industry - Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components for Transfusion to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV*. Given the complexity of having to implement testing that is currently available from only one laboratory, a realistic and adequate amount of time should be allowed for full implementation. A full twelve months for implementation may be appropriate, since implementation of NAT may require several custom interfaces, e.g., with 510(k) cleared computer systems, etc. Alternatively, manufacturers who have assumed full responsibility for NAT testing should be given a date, i.e., within a given number of months of the date of the final guidance document, by which a BLA for their NAT testing process should be submitted.

**Requirement for a Prior Approval Supplement**

The requirement to submit a prior approval supplement is not consistent with the document *Guidance for Industry - Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture*, where examples of changes in contract testing laboratories that perform infectious disease testing are provided. The example of a change in infectious disease testing that would require a CBE-30 supplement, i.e., the use of or change to, an FDA registered contract testing laboratory currently engaged in blood product testing, is the best match to the only option for licensed NAT that is currently available. Since the NGI laboratory itself has been licensed for HIV-1 and HCV NAT, and the test has not been licensed as a kit that can be implemented in other laboratories, the example provided for a prior approval supplement, i.e., the use of, or change to, a new facility or any facility not previously engaged in blood product testing, is not as good a match.

Reporting the change in NAT testing (i.e., to use NGI as a contract laboratory) as a CBE-30 supplement would also be consistent with the recommendation as stated in the more recent *Draft Guidance for Industry - Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components for Transfusion to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV.*

**Elimination of HIV-1 p24 Antigen Testing**

The guidance states that the FDA may consider not requiring HIV-1 p24 testing of Source Plasma if establishments implement NATs that are more sensitive than HIV-1 p24 tests. The draft guidance also mentions that the prior approval supplement submitted by Alpha Therapeutic Corporation for use of the NAT systems developed by NGI for HIV-1 and HCV had been approved. It should be noted that this approval also allowed the use of the approved NAT as an alternative to currently licensed HIV-1 p24 antigen tests for screening Source Plasma. It can therefore be inferred that the licensed NAT for HIV-1 is at least as sensitive as the HIV-1 p24 tests. The status of the licensed NAT for HIV-1 should be clearly stated in the guidance document.

**Continued Testing Under an IND**

The draft guidance document states that manufacturers who are currently investigating other NATs for Source Plasma collections may continue use of alternative NAT testing under an approved IND provided that the manufacturer implements the approved test by the required date. This will result in duplicate testing, and will create problems in managing samples, test results, units of Source Plasma, and the donors. As previously mentioned, manufacturers who may be well into the process of licensing their own NAT should be granted consideration in this guidance document, and if licensure of their NAT is imminent, implementation of the currently licensed NAT, which maybe be needed for only a short period of time, should not be required.

**Labeling Statements**

The *Draft Guidance for Industry - Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components for Transfusion to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV* provides excellent direction regarding labeling statements for blood products for transfusion that have been tested using a licensed NAT. Comparable guidance should be included in the equivalent document for Source Plasma. The proposed labeling statement for blood components prepared from Whole Blood or blood components for further manufacture into injectable or non-injectable products, i.e., "Nonreactive by licensed Nucleic Acid Tests for HCV RNA and HIV-1 RNA performed on pooled samples," is equally applicable to Source Plasma.

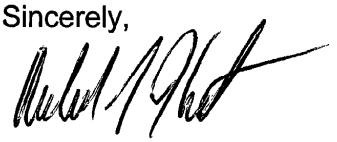
In addition, guidance regarding labeling statements for finished products manufactured from Source Plasma that has been tested using licensed NAT should be provided. This should include the mechanism for submitting the labeling statements, and whether any other license

supplements for finished products will be needed. This is especially appropriate since Source Plasma by definition is intended only for further manufacturing use, and in terms of statements related to safety that can be attributed to testing such as NAT, the qualities of the Source Plasma are an intrinsic part of the qualities of the finished product.

Aventis Bio-Services appreciates the opportunity to comment on this important draft guidance document, and to partner with the FDA in working to improve the safety of plasma derivatives.

Please do not hesitate to contact me if you have any questions regarding these comments.

Sincerely,



Robert J. Kratzel, Ph.D., M.B.A.
Director, Regulatory Affairs

KING
(610) 878-4020
AVENTIS BEHRING
1020 FIRST AVENUE
KING OF PRUSSIA PA 19406

LTR 1 OF 1

**SHIP TO:**
DOCKERS MANAGEMENT BRANCH (HFA-305)
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